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Remission Maintenance Therapy in Acute Myelogenous Leukemia

STEPHEN H. EMBURY, MD; LAURENCE ELIAS, MD; PHILIP H. HELLER, MD, PhD; CHARLES E. HOOD, MD; PETER L. GREENBERG, MD, *and* STANLEY L. SCHRIER, MD, *Stanford*

Because no conclusive evidence as to the efficacy of maintenance chemotherapy in acute myelogenous leukemia (AML) existed, a study to obtain such information was done. Twenty-six adult patients with AML in whom complete remission had been achieved following induction chemotherapy were randomly assigned to receive either maintenance chemotherapy consisting of cytarabine and 6-thioguanine for two days each month or to receive no maintenance therapy. The data showed a significant difference in remission duration between the two groups, with median remission lengths for the maintained and unmaintained groups being 10.3 and 6.7 months, respectively ($p<.05$). In 46 percent of the maintained patients there were remissions lasting longer than 11 months, whereas in none of the unmaintained patients was there such a prolonged remission. No significant drug-induced toxicity was observed. That the prolonged exposure to these chemotherapeutic agents, which were also used in our induction program, did not adversely affect the rate of successful reinduction therapy was shown by identical 50 percent complete remission rates for second inductions in both groups. In patients with palpable splenomegaly at the time of diagnosis, there was no prolongation of remission with maintenance therapy. These data indicate the potential utility of maintenance chemotherapy for prolonging remission duration in acute myelogenous leukemia.

DESPITE a lack of conclusive evidence, it has been assumed that maintenance chemotherapy is useful in the management of acute myelogenous leukemia (AML). This assumption is related to the established effectiveness of such therapy in acute lymphocytic leukemia.[1,2] However, the single controlled study suggesting efficacy of maintenance therapy in AML[3] had an exceedingly brief remission duration in the unmaintained group and failed to show this advantage when the dose of the chemotherapeutic agent, cytarabine, was increased. Other controlled studies of AML maintenance therapy[4] failed to show an advantage of mercaptopurine or of combination therapy with vincristine, methotrexate, mercaptopurine and prednisone compared with no maintenance therapy. Owing to a lack of concurrently unmaintained controls in recent studies,[5-7] it has

From the Division of Hematology, Stanford University School of Medicine, Stanford, California, and the Palo Alto Veterans Administration Hospital, Palo Alto.

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Reprint requests to Stephen Embury, MD, Division of Hematology, S-161, Stanford University School of Medicine, Stanford, CA 94305.

ABBREVIATION USED IN TEXT
AML = acute myelogenous leukemia

been difficult to determine if the improved results have been the result of heavy maintenance therapy or modern induction programs. Recent reports on maintenance immunotherapy and chemotherapy lack untreated control groups and do not show a pronounced advantage of this type of treatment compared with chemotherapy alone.[8]

In order to determine if the implied theoretical advantage of maintenance therapy[9] outweighed the risk of its toxicity, we carried out a study comparing maintenance chemotherapy with no maintenance therapy in patients with AML in complete remission. When complete remission was documented, patients received a course of consolidation therapy which consisted of cytarabine and 6-thioguanine given over two days. The group receiving maintenance therapy received monthly treatment identical to consolidation therapy, while the other group received no further chemotherapy.

Materials and Methods

Patient Group

The patients in the study of maintenance therapy included 22 adults with AML (acute myeloblastic, monocytic or myelomonocytic leukemia), two with promyelocytic leukemia and two who had subacute myelogenous leukemia before conversion to classical AML. Patients had received no previous therapy for AML and there had been complete remission with standardized induction regimens supervised by the Stanford University Hematology Division. The median age of patients entered on the study was 45 years, with a range of 18 to 72 years.

Remission Induction Regimen

The induction program was modified from the programs of Clarkson, Gee and colleagues[6,7,10] by the addition of daunarubicin. With minor modifications therapy was administered as follows: daunarubicin, 60 mg per sq meter by rapid intravenous infusion, was given on the first day. This was followed in 12 hours by cytarabine, 3 mg per kg of body weight by rapid intravenous infusion, and 6-thioguanine, 2.5 mg per kg of body weight given orally. Administration of the last two agents was continued every 12 hours until biopsy-proven marrow hypoplasia was achieved. A second dose of daunarubicin between days 7 and 10 was nearly always given, the dose varying, depending on the cellularity of a marrow biopsy specimen. Changes in therapy from the original program[10] were undertaken so as to shorten the treatment program and decrease the time at risk from severe neutropenia and thrombopenia. That this was achieved is reflected in the shorter treatment period required to reach hypoplasia with the current drug program (15.4 ± 7.0 days, mean $\pm$ SD) compared with our earlier regimen[11] employing only a single daily dose of cytarabine and 6-thioguanine (23.8 ± 12.3 days) ($p < .01$, Student's t test).

During induction, patients received general ward care and oral mycostatin fungal prophylaxis. The induction and support therapy was administered under general ward care by the Stanford University medical house staff. Combination antibiotics were administered for documented or suspected sepsis, and amphotericin B was used in patients with proven or suspected fungal infection. Prophylactic random donor platelet transfusions were given when the platelet count descended below 10,000 per cu mm. Patients showing no rise in platelet count following random donor platelet transfusion received, when possible, platelets from related donors in order to obtain at least partial histocompatibility. No patient in this study received granulocyte transfusion or barrier isolation.

The characteristics of this induction program are exemplified by the courses of the last 30 consecutive patients admitted to the induction protocol, which included 18 of the 26 patients evaluated in the maintenance study. In 19 patients (63 percent) complete remission was achieved and in 8 (27 percent) there was partial remission. The induction is characterized by a period of chemotherapy to hypoplasia of 15.4 ± 7 days (mean $\pm$ SD), a period from marrow hypoplasia to rising platelet or neutrophil counts of 12.3 ± 5.5 days, a neutropenic (absolute neutrophil count < 500 per cu mm) period of 26.3 ± 7.5 days, a thrombopenic (nontransfused platelet count $< 10{,}000$ cu mm) period of 23.6 ± 11.2 and an incidence of presumed and documented sepsis of 97 percent (one of 30 inductions was without sepsis). The median age of these last 30 patients is 50.5 years, with a range of 16 to 74 years.

Consolidation Therapy

Consolidation therapy was given at the time complete remission was documented, usually three to four weeks after sustained rise in either platelet or neutrophil count began. The criteria for complete and partial remission have been previously described.[12] Consolidation therapy consisted of four four-hour infusions of cytarabine, 75 mg per sq meter, given every 12 hours and two oral doses of 6-thioguanine, 2.5 mg per kg of body weight, given every 24 hours.

Maintenance Therapy

At the time of consolidation informed consent was obtained and patients were randomly assigned to a group to receive either a monthly course of maintenance therapy identical to the consolidation therapy or to a group to receive no maintenance therapy. Patients in both groups were evaluated identically, in that they were seen monthly for thorough clinical evaluation, including complete blood count, platelet count and tests of bone marrow aspirate. This study was approved by the Stanford Medical Center Human Experimentation Committee.

Analysis

Duration of complete remission was calculated from the time of consolidation and marrow documentation of complete remission to the time when clinical relapse occurred. In five patients who did not receive consolidation, remission was dated from the time of marrow documentation of complete remission. Survival was dated from time of diagnosis to death with the exception of the two patients with subacute myelogenous leukemia in whom survival was dated from the time of their conversion to classical AML.

Advice on statistical analysis was given by Dr. Rupert Miller and analyses were by the two-tailed modified Wilcoxon test,[13] unless otherwise specified.

Results

Thirteen patients were randomly assigned to each study group. There is a distinct advantage of the maintenance program used, as shown by the significantly longer duration of remission for patients in this group (Figure 1, Kaplan-Meyer Actuarial Plot) ($p<.05$). The median duration of remission for the maintained and nonmaintained groups were 10.3 and 6.7 months, respectively. Furthermore, there were significantly more long

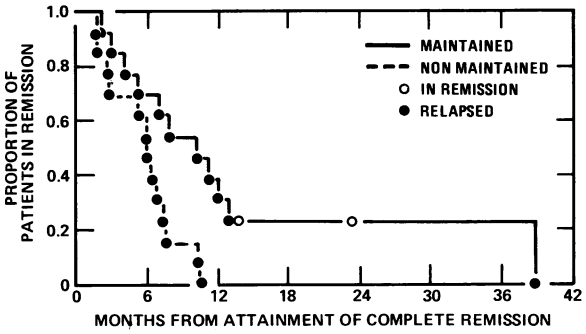

Figure 1.—Remission duration of patients randomly assigned to maintenance or no maintenance therapy.

remissions (defined as lasting at least 11 months following consolidation) in the maintained group as compared with the nonmaintained group, 46 percent versus 0 percent ($p<.05$, x^2 corrected) (Figure 1). Through various protocol misadventures, five patients in the group not receiving maintenance therapy failed to receive consolidation therapy. Comparison of this subgroup to the remainder of the nonmaintained group showed no difference in remission duration ($p>0.1$). Comparison of the consolidated patients in the maintained (13 patients) and nonmaintained (8 patients) groups indicated that the maintained group still had a significantly longer duration of remission ($p<.04$).

No drug-induced renal or hepatic toxicity or significant cytopenia was observed. Nausea and vomiting were seen only during the administration of chemotherapy, usually with the first infusion of cytarabine.

Since long remissions occur so infrequently in AML the incidence of long remissions was analyzed with respect to the following clinical features: age at presentation, sex, presence of splenomegaly, lymphadenopathy, leukocyte count, blast count, platelet count, fever, number of days of chemotherapy required to reach hypoplasia, doses of drugs required to reach hypoplasia, and number of days from documented hypoplasia to ascending platelet or neutrophil count. Our analysis showed that only presenting palpable splenomegaly was useful for predicting remission duration. In the maintained group, in which all long remissions occurred, the spleen was palpable in none of the six patients with long remissions, whereas in five of the nine patients with shorter remissions there were palpable spleens ($p<.05$). All nonmaintained patients had short remissions, six with palpable splenomegaly and seven without. Combining maintained and nonmaintained

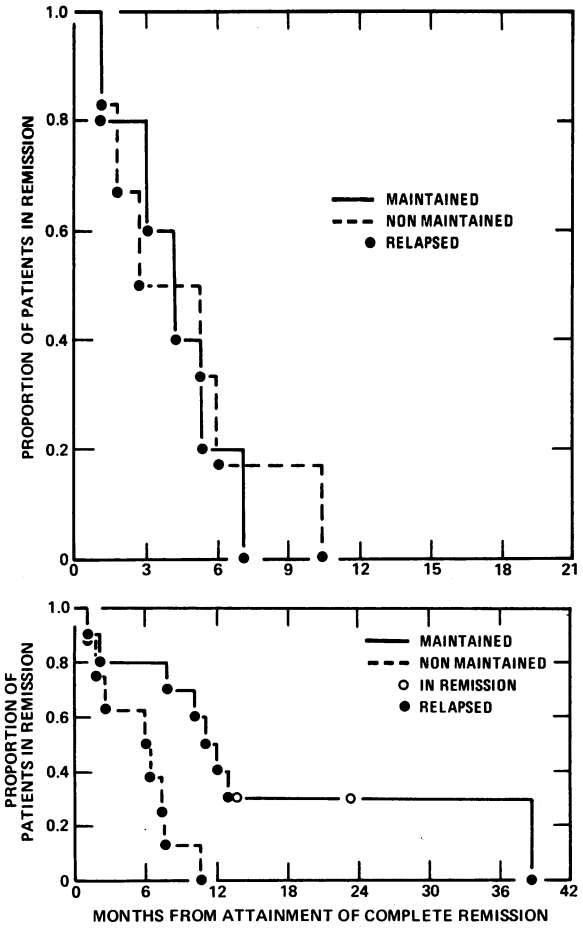

Figure 2.—Remission duration of the maintained and nonmaintained patients. **Upper,** with palpable splenomegaly at the time of diagnosis. **Lower,** without palpable splenomegaly at the time of diagnosis.

groups showed that palpable splenomegaly was of negative prognostic value for long remission ($p<.04$). The further significance of presenting splenomegaly is shown by analyzing the result of maintenance chemotherapy on remission length in the combined groups with and without splenomegaly (Figure 2). In those patients without splenomegaly there were longer remissions if maintenance therapy was given, whereas in those patients with splenomegaly remissions were short whether or not maintenance therapy was given ($p<.05$).

Analysis of the results of subsequent remission inductions with the same induction regimen according to whether or not the patient had received maintenance chemotherapy during the first remission showed no difference between the two groups. Of the eight previously maintained patients receiving a second course of induction, complete remission was achieved in four (50 percent), and of the

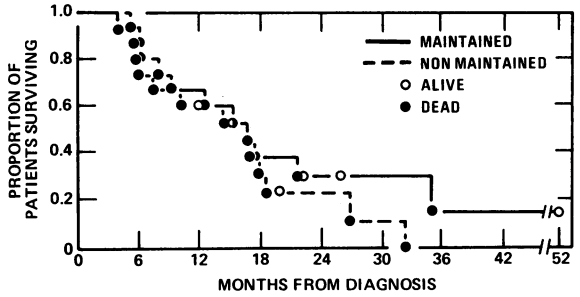

Figure 3.—Duration of survival of the patients receiving or not receiving maintenance therapy.

12 previously unmaintained patients receiving reinduction, there was complete remission in six (50 percent).

Four additional randomly assigned patients (two in each group), were not included in analysis of remission duration because they relapsed four to five weeks after consolidation, before the first maintenance course was due, and in this analysis their brief remissions would not have reflected differences in the two approaches. These four patients were, however, included in the analysis of survival where no difference was noted between the 15.4-month median survival of the maintained group and the 15.6-month median survival of the nonmaintained group ($p>.9$) (Figure 3).

Discussion

This study has shown that a nontoxic maintenance chemotherapy regimen prolongs the duration of remission in patients with AML. Median remission duration of maintained patients was 10.3 months, as compared with 6.7 months for patients receiving no maintenance therapy. Of the patients receiving maintenance therapy there were remissions lasting more than 11 months in 46 percent, as compared with no such long remission in the unmaintained group. Compared with a more intensive maintenance chemotherapy regimen,[6,7] this program entailed fewer days of therapy, was less myelotoxic and produced a comparable remission duration, but it yielded shorter overall survival. Although the cause for the shorter survival is unclear, the similar remission length implies that the difference lies not in the maintenance program, but in different results of salvage therapy following relapse. This difference may represent a variable severity of relapse which in turn may be a function of the intensity of earlier induction and consolidation therapies.

Current reports of long remission duration[5-8,14,15] employ both high dose maintenance therapy and modern induction programs, making it difficult to discern which modality is responsible for the improved results. A recent preliminary report showed no difference in remission duration or survival in comparing no maintenance therapy with high dose maintenance therapy.[16] Other comparative controlled data regarding the usefulness of maintenance therapy in AML are found only in studies conducted before the development of modern induction programs and fail to conclusively resolve the issue.[3,4]

The finding of significantly more remissions lasting longer than 11 months occurring in our group receiving maintenance therapy raises the possibility that such therapy may enhance the potential for prolonged remission. Although long remissions and survivals were occasionally seen in AML before modern therapy regimens,[17-21] an increasing incidence of such events[7,14] raises the possibility that certain programs are capable of achieving this effect. Further efficacy of postinduction therapy in remission prolongation has recently been reported using late intensification chemotherapy.[22]

The suspected efficacy of maintenance therapy is based not only on the advances seen in acute lymphocytic leukemia,[1,2] but also on several theoretical arguments. It has recently been shown that morphologically normal peripheral leukocytes from patients with AML in remission contain RNA-dependent DNA polymerase, the marker previously believed to have been specific for leukemic cells.[23] As the authors suggest, chemotherapy may be instrumental in the transition of the leukemic clone into a nonneoplastic clone which expresses only this viral function merely as a marker. A further theoretical consideration favoring maintenance therapy would argue from the kinetic viewpoint that the morphologically undetected leukemic cells persisting in remission have a high growth fraction concomitant with a reduced leukemic cell burden[9] and are thus more susceptible to cell cycle stage specific agents.[24] Assuming similar kinetics for leukemic and normal precursor cells, intermittent infusions were chosen because previous studies with several of our patients had shown that this type of therapy was capable of causing pronounced reduction in the number of granulocytic progenitor cells in DNA synthesis.[25]

We chose a maintenance program that was not significantly myelotoxic because there was no previous evidence showing efficacy of maintenance therapy. The program chosen required two days per month in hospital and permitted nearly normal activity, a goal which has been recently emphasized.[26] Furthermore, theoretical arguments could be advanced for a potential detrimental effect of chemotherapy on AML in remission if such therapy were to disturb a balance between emergent normal "feeder" stem cells and leukemic "sleeper" stem cells, postulated to exist during remission.[27]

Patients with palpable splenomegaly did not respond to maintenance chemotherapy with lengthened remission. However, in a study employing more intensive chemotherapy,[7] splenomegaly had been found to be of no prognostic significance. These contrasting observations, along with the suggestion that splenectomy during remission of childhood AML prolongs remission,[28] indicate that methods of reducing the splenic tumor burden to the point where it is no longer a determinant of remission length bear further investigation.

It has been shown that prolonged cytarabine therapy can induce elevation of cytidine deaminase levels concomitant with resistance to the drug.[29] The fact that reinduction with our DAT program following initial relapse produced identical remission rates in those who had received maintenance therapy and those who had not, indicated that the maintenance regimen does not uniformly induce clinically significant drug resistance.

In this study, the efficacy of maintenance therapy was not reflected by increased survival. However, since the patients were not managed in a consistent manner following relapse (some patients even electing to undergo no further induction therapy), the effect of maintenance therapy on survival is difficult to evaluate in this study, and the data that can be evaluated end with the first relapse.

REFERENCES

1. Frei E III: Combination cancer therapy: Presidential address. Cancer Res 32:2593-2607, Dec 1972

2. Simone J: Acute lymphocytic leukemia in childhood. Semin Hemat 11:25-39, Jan 1974

3. Ellison RR, Holland JF, Weil M, et al: Arabinosyl cytosine: A useful agent in the treatment of acute leukemia in adults. Blood 32:507-523, Oct 1968

4. Holland JF, Glidewell O: Complementary chemotherapy in acute leukemia, *In* Mathe G (Ed): Recent Results in Cancer Research: Advances in the Treatment of Acute (Blastic) Leukemias. New York, Springer-Verlag, 1970, pp 95-108

5. Bodey GP, Coltman CA, Freireich EJ, et al: Chemotherapy of acute leukemia. Arch Intern Med 133:260-266, Feb 1974

6. Clarkson BD: Acute myelocytic leukemia in adults. Cancer 30:1572-1582, Dec 1972

7. Clarkson BD, Dowling MD, Gee TS, et al: Treatment of acute leukemia in adults. Cancer 36(suppl):775-795, Aug 1975

8. Powles RL: Immunotherapy in the management of acute leukemia. Br J Haemat 32:145-149, Feb 1976

9. Saunders EF, Lampkin BC, Maurer AM: Variation of proliferative activity in leukemic cell populations of patients with acute leukemia. J Clin Invest 46:1356-1363, Aug 1967

10. Gee TS, Yu K-P, Clarkson BD: Treatment of adult acute leukemia with arabinosyl cytosine and thioguanine. Cancer 23: 1019-1032, May 1969

11. Poth JL, Johnson PK, George RP Jr, et al: Therapy of acute myelocytic leukemia. Calif Med 117:1-11, Dec 1972

12. Hewlett JS, Battle JD Jr, Bishop RC, et al: Phase II Study of A-8103 (NSC-25154) in acute leukemia in adults. Cancer Chemother Rep 42:25-28, Nov 1964

13. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52:203-223, 1965

14. Grozea PN, Bottomley RH, Shaw MT, et al: The role of cytosine arabinoside maintenance in acute nonlymphoblastic leukemia. Cancer 36:855-860, Sep 1975

15. Leukemia and hematosarcoma cooperative group of the European Organisation for Research on the Treatment of Cancer (EORTC)—A second cooperative trial of remission induction (by cytosine arabinoside given every 12 hours, or C.A.R. and thioguanine or C.A.R. and daunarubicine) and maintenance therapy (by C.A.R. or methylgag) in acute myeloid leukemia. Eur J Cancer 10:413-418, Jul 1974

16. Lewis JP, Linman JW, Pajak TF, et al: Effect of "maintenance" chemotherapy on survival in adults with acute nonlymphocytic leukemia. Clin Res 24:158A, Feb 1976

17. Burchenal JH: Features suggesting curability in leukemia and lymphoma, *In* Zafaronetis CJ (Ed): Proceedings of International Conference on Leukemia-lymphoma. Philadelphia, 1968, pp 93-104

18. Fairbanks VF, Shanbrom E, Steinfeld JL, et al: Prolonged remissions in acute myelocytic leukemia in adults, JAMA 204:574-579, May 13, 1968

19. Jacquillat C, Weil M, Gemon MF, et al: Evaluation of 216 four-year survivors of acute leukemia. Cancer 32:286-293, Aug 1973

20. Jacquillat C, Weil M, Tanzer J, et al: Les très longues rémissions complètes des leucémies aigues. A propos de 65 observations de leucémies aigues dont la durée a dépassé 4 ans. Presse Med 78:253-256, Jan 31, 1970

21. Till MM, Hardisty RM, Pike MC: Long survivals in acute leukemia. Lancet 1:534-538, Mar 10, 1973

22. Bodey GP, Freireich EJ, Gehan E, et al: Late intensification therapy for acute leukemia in remission. JAMA 235:1021-1025, Mar 8, 1976

23. Viola MV, Frazier M, Wiernik PH, et al: Reverse transcriptase in leukocytes of leukemic patients in remission. N Engl J Med 294:75-80, Jul 8, 1976

24. Skipper HE, Schabel HM Jr, Wilcox WS: Experimental evaluation of potential anticancer agents XX!—Scheduling of arabinosylcytosine to take advantage of its S-phase specificity against leukemia cells. Cancer Chemother Rep 51:125-141, Jun 1967

25. Greenberg P, Bax I, Mara B, et al: Alterations of granulopoiesis following chemotherapy. Blood 44:375-383, Sep 1974

26. Burge PS, Prankerd TAJ, Richards JDM, et al: Quality and quantity of survival in acute myeloid leukemia. Lancet 2: 621-624, Oct 4, 1975

27. Killman S: Acute leukemia: Development, remission-relapse pattern, relationship between normal and leukemic hemopoiesis, and the "sleeper to feeder" stem cell hypothesis. Ser Haemat 1: 103-128, 1968

28. Fleming I, Simone J, Jackson R, et al: Splenectomy and chemotherapy in acute myelocytic leukemia of childhood. Cancer 33:427-434, Feb 1974

29. Stewart CD, Burke PJ: Cytidine deaminase and the development of resistance to arabinosyl cytosine. Nature (New Biol) 233:109-110, Sep 22, 1971

Initial Screening in Patients with Blood in Stool

During a routine rectal examination, a positive stool guaiac is found. What procedures should be followed to discover the source of the bleeding?

I think the initial screening that we would do probably would be sigmoidoscopy followed by barium enema. Certainly lesions in the upper tract also bleed, certainly the teeth can bleed and the nose can bleed and give a positive stool guaiac. We start with a physical examination of the patient and evaluation, and then listen to symptomatic history. And if we don't have any symptomatic history and no potential lesions, then I think we probably would start from the bottom up and then work down from the top. And I think if there was no lesion on any of our screening tests and blood persists in the stool . . . then at that point, one might consider an endoscopic evaluation, be it colonoscopy or upper gastrointestinal endoscopy.

We're engaged in a program of trying to evaluate just this problem. And our procedure is . . . a physical examination, protoscopy barium enema and flexible colonoscopy. We've had an extremely low incidence of false positives. We found significant pathology in just about everybody who had a repeat positive Hemoccult® slide. And strangely, very few of these cases were diverticular disease; most of them were polyps or cancer, or both.

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